REMARKS

Claim 7 has been amended to remove the recitation of "or a fragment thereof." Support for this amendment is found in the specification at, for example, page 9, lines 5-7 and original claim 27. *See*, *In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

Claims 8 and 9 have been amended to clarify that the at least 20 or 30 bases are "of the coding region" of SEQ ID NO:2, respectively. Support for these amendments is found in the specification at, for example, page 3, lines 15-19, SEQ ID NO:1, page, 9, lines 7-9, and original claims 8 and 9. (*Id.*).

Claim 36 was amended for clarity to indicate that the recited polypeptide is SEQ ID NO:1 or a fragment thereof.

Claims 37-40 have been added. Claim 37 recites that the nucleic acid sequence "comprises a fragment of the coding region of SEQ ID NO:2 selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10." Claims 38-40 further identify the fragment recited in claim 37. Support for these claims is found in the specification at, for example, page 9, lines 19-26 and page 18, line 24 - page 19, line 29.

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments respectfully is requested.

§101 Rejection

Claims 6-36 were rejected under 35 U.S.C. §101 as lacking "patentable utility." (Paper No. 11 at 3). In making the rejection, the Examiner asserts that the

claims are "not supported by either a specific and substantial utility." (*Id.*). To support this position, the Examiner asserts that the specification discloses that SEQ ID NO:1 has β,β-carotene 15,15'-***di***oxygenase activity but that "Applicants state that subsequent studies revealed the function of the enzyme represented by SEQ ID NO:1 is a β,β-carotene 15,15'-***mono***oxygenase ...." (*Id.*). The Examiner then concludes that "the specification does not teach the function of SEQ ID NO:1." (*Id.*).

The Examiner further asserts that "the β,β-carotene 15,15'-monooxygenase activity of SEQ ID NO:1 is unpredictable in the art because SEQ ID NO:1 has homology with polypeptides with β,β-carotene 15,15'-dioxygenase activity. (*Id.*). The Examiner also asserts that "[t]hese claims amount to a polypeptide with unknown function and a polypeptide with unknown and unpredictable function has no utility." (*Id*). The Examiner then contends that "there is no specific, substantial, or credible utility that is well known, apparent or implied by the relationship of the instant polynucleotide to the polynucleotide encoding SEQ ID NO:1." (*Id.*).

For the reasons set forth below, this rejection respectfully is traversed.

Initially, we note that the Examiner bears a heavy burden for rejecting a claim under §101. The PTO's own Utility Examination Guidelines require for a *prima facie* case of lack of utility that an Examiner provide:

(a) An explanation that clearly sets forth the reasoning used in the rejection;

(b) Support for factual findings relied on in reaching the conclusion; and

(c) An evaluation of all relevant evidence of record.

66 FR 1092, 1098 (January 5, 2001). This the rejection does not do.

For example, in the section entitled "Response to Amendment," the Examiner asserts that "the starting material needs to be taught because there are many pathways leading to the production of vitamin A without any teachings on the substrate specificity." (Paper No. 11 at 2). This assertion is unclear because the starting material, *i.e.*, the polypeptide having the amino acid sequence of SEQ ID NO:1 is clearly identified in the specification and activity assays are also provided.

Next, the Examiner asserts that SEQ ID NO:1 has homology with polypeptides with β,β-carotene 15,15'-dioxygenase activity. (*Id.* at 3). The rejection, however, is devoid of any sequence comparison that would provide factual support for such an assertion.

Still further, the rejection provides no evidence that the entirety of the specification was considered prior to making this rejection. At most, the rejection boldly asserts that "the claims amount to a polypeptide with unknown function and a polypeptide with unknown and unpredictable function has no utility." (*Id.*). Thus, because the rejection is unclear, factually deficient, and does not consider all of the evidence of record (*i.e.*, the specification), the rejection is insufficient as a matter of law and PTO procedure. For this reason alone, the rejection should be withdrawn.

Notwithstanding the legally insufficient nature of the rejection, we note that the utility requirement is complied with if (1) there is disclosure that the claimed invention is "useful for ***any particular practical purpose*** ... and the assertion would be

considered credible by a person of ordinary skill in the art; (2) that the asserted utility is specific and substantial, *i.e.*, that it is not a throw-away, insubstantial, or nonspecific utility; and (3) that at least one credible assertion of a specific and substantial utility for each claimed invention is provided. (*See* MPEP §2107 at 2100-20 (8th Ed. August 2001)). Thus, an assertion of utility must meet a three-prong test – it must be practical, substantial, and credible.

To determine compliance with this three-prong test, the specification, including the claims must be analyzed. For the Examiner's convenience, we reproduce from the specification examples of the types of utility clearly disclosed therein:

(1) Statements of Utility in Specification

> ***A process is also provided for the production of vitamin A.*** This process includes enzymatically cleaving β-carotene by a polypeptide as described above. (p. 2, lines 21-22).
>
> Figure 8 is a chromatogram demonstrating that the peak from Fig. 7 representing ***the only product of the enzymatic cleaving is retinal.*** (p. 5, lines 8-9).
>
> ***The nucleic acid sequences of the present invention code for a protein of the present invention*** or a part thereof. (p. 9, lines 7-8).
>
> ***The nucleic acid sequences of the present invention can be used as antisense RNA probes*** for *in situ* hybridization. (*Id.* at lines 16-17).
>
> Another diagnostic option is ***quantification of mRNA by RT-PCR.*** (p. 10, line 11).
>
> Since the protein has been expressed and a method for purifying the protein is described in detail in the examples ***the person skilled in the art can use the protein or peptides derived from the amino acid***

sequences in order to generate antibodies which specifically react with the protein. (*Id.* at lines 15-18).

The antibodies can also be used in laboratory methods like Western blots or immuno-precipitations. Preferably such antibodies can be used in immunohistochemistry to detect epitopes of β,β-carotene 15,15'-dioxygenase in embedded or fixed tissues or cells of any species of interest. (p. 11, lines 6-9).

A preferred source of β-carotene is the alga *Dunaliella bardawil* which has a high endogenous level of β-carotene. Suitable algae can be grown conveniently and β-carotene can be purified therefrom at rather low cost. ***The carotene can be conveniently cleaved enzymatically using a protein of the present invention.*** (p. 11, lines 15-20).

The vector having the gene and the other required genetic structures is then introduced into suitable host cells by well-known methods like transformation, transfection, electroporation or microprojectile bombardment. ***Depending on the host cell it may be preferred to stably integrate the gene coding for a protein of the present invention into the genome of the host cell. The cells obtained by such methods can then be further propagated and if the cell is a plant cell it is possible to generate therefrom transgenic plants***. (p. 12, lines 6-12).

D) Activity screening of the chicken cDNA library:

90 of the above pools were tested for activity in a transactivation assay based on the detection of retinoic acid which is produced in eukaryotic cells after β-carotene cleavage. The principle of the activity test is shown in Fig. 2.

5 µg of DNA from each pool were transfected with 20 µg of lipofectin (Life Technologies) into a reporter cell line bearing a luciferase reporter plasmid with a

RARE (retinoic acid response element) in front of the tk promoter (Herpes simplex thymidine kinase promoter). Transfections were done for 7 hours under serum free conditions. After 7 hours the transfection mix was removed and RPMI medium with 10% charcoal treated FCS (fetal calf serum) was added. After 20 hours of incubation β-carotene (β-carotene 10% CWS, F. Hoffmann-La Roche Ltd.) or a placebo formulation were added to the culture medium to a final β-Carotene concentration of 5 µM. Incubation was continued for 18 hours. Then cells were washed with PBS, and luciferase expression was measured after substrate addition with a nitrogen cooled slow scan CCD camera (AstroCam Ltd.) Exposure time usually was 8 min. Analysis was done with the Image Pro Plus 3.0 software package (Media Cybernatic, Maryland). 3 pools were strongly positive, 7 pools showed weaker, but detectable activity.

One of the positive pools was plated on a square agar plate. 2 filters (nylon membranes, Gene Screen, NEN Research Products, Boston) were processed and screened with the radioactively ((α^{32}P) dATP, Amersham) labeled 597 bp PCR-fragment. From 9500 colonies screened, 14 were double positive. From 36 colonies picked, 5 showed the same pattern after restriction site analysis. 2 clones were sequenced from the 5' end and the original 51 bp sequence was found. Subsequently the whole cDNA was sequenced and confirmed twice.

* * *

The obtained cDNA sequence is shown in Figure 3 and the amino acid sequence deduced therefrom in Figure 4.

Figure 4 shows the derived amino acid sequence having 526 residues.

(p. 21, line 23 - p. 22, line 29).

After expression in *E. coli* and purification over a metal chelate column, ***the protein shows cleavage***

activity with β-carotene as substrate. Retinal was the only product detected by HPLC after incubation with β-carotene. No apocarotenals or other metabolites were found. This was proved by HPLC analysis as shown in Figs. 7 and 8.

(p. 25, lines 9-12).

(2) Statements of Utility in Original Claims

1. ***An isolated polypeptide having β,β-carotene 15,15'-dioxygenase activity comprising SEQ ID NO: 1*** or a polypeptide having β,β-carotene 15,15'-dioxygenase activity and being at least 60% homologous to SEQ ID NO: 1 as determined by the Wisconsin Sequence Analysis Package GCG, Version 9.1 (1997).

18. ***A process for the production of vitamin A comprising enzymatically cleaving β-carotene with a polypeptide according to claim 1***.

Applying the three-prong test, we note that a practical utility is one that provides some immediate benefit to the public. *Nelson v. Bowler*, 206 USPQ 881, 883 (CCPA 1980). The following are representative assertions of practical utility set forth in the specification for the claimed invention:

1. A process for the production of vitamin A;
2. producing an enzymatic cleavage product, which is retinal;
3. the nucleic acid sequences can be used as RNA probes;
4. quantification of mRNA by RT-PCR;
5. generation of antibodies;
6. enzymatically cleaving carotene;

7. generation of transgenic plants;

8. cleavage of β-carotene; and

9. production of vitamin A by cleaving β-carotene.

It is respectfully submitted that any one of these ***nine*** asserted utilities are sufficient to support the practical utility requirement under §101. For example, the asserted utility of using one of the polypeptides of the present invention to cleave β-carotene to form vitamin A is of immediate benefit to the public because vitamin A is an essential vitamin required by man and animals. (*See e.g.*, Specification at p. 5, lines 13-17). Nothing more is required to meet the "practical" utility prong of §101.

A specific utility is specific to the subject matter claimed. (*See* MPEP §2107.01 at 2100-32). Here, the specification asserts that "[a] process is provided for the production of vitamin A" (p. 2, lines 21-22) and that "[t]he carotene can be conveniently cleaved enzymatically using a protein of the present invention" (p. 11, lines 18-19). The claims are directed to specific isolated nucleic acid sequences which encode "a protein of the present invention," which is used to cleave carotene in the production of vitamin A. Thus, the asserted utility is specific to the subject matter claimed.

In the section entitled "Response to Amendment," the Examiner asserts that the identification of SEQ ID NO:1 as a participant in the pathway leading to the production of vitamin A is insufficient to meet the utility requirement. (Paper No. 11 at 2). The Examiner asserts that "[t]he starting material needs to be taught because there are many pathways leading to the production of vitamin A without any teachings on the

substrate specificity." (*Id.*). The Examiner further asserts that "cleavage of β-carotene by β,β-carotene 15,15'-***di***oxygenase results in two moles of retinal. This reaction will have ***different results*** with a polypeptide having the current identification of β,β-carotene 15,15' ***mono***oxygenase activity." (*Id.*).

It is respectfully submitted that the Examiner's analysis is not well taken. First, the Examiner asserts that because there are multiple pathways leading to vitamin A production, "the starting material needs to be taught." As noted above, the starting material is taught. The correct amino acid sequence of the enzyme of the present invention is disclosed as SEQ ID NO:1. With this sequence, the enzyme or "staring material" is fully disclosed.

The specification also provides an "activity assay" for the "enzyme preparation." (p.14, lines 8-9). With this activity assay in hand any enzyme preparation may be tested to determine if β,β-carotene, retinal, apo-β-carotenals, and retinoic acid is formed which products may be correlated to the value of vitamin A. (*Id.* at lines 22-28). Thus, preparing an enzyme having the amino acid sequence of SEQ ID NO:2, and running the enzyme in the disclosed assay confirms the enzyme's utility in the production of vitamin A.

Second, the misnaming of the enzyme in the specification does ***not*** alter its correctly disclosed substrate, substrate specificity, and cleavage productions. Thus, whether the enzyme having the amino acid sequence of SEQ ID NO:1 is called a "monooxygenase" or a "dioxygenase" is irrelevant to the data presented in the specification regarding the observed - and unchanged - physical/kinetic characteristics

of the polypeptide. Thus, the Examiner's assertion of "different results" is an impossibility because the enzyme has not changed.[1]

A substantial utility defines a real world use. (MPEP §2107.01 at 2100-32). The MPEP states that any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient ...." (*Id.* at 2100-33). And, a disclosure that identifies a particular biological activity of a compound and explains how that activity can be utilized in a particular therapeutic application of the compound does contain an assertion of specific and substantial utility for the invention. (MPEP 2107.02 at 2100-38).

Thus, the assertion in the specification of any of the ***nine*** utilities set forth above meet the "public benefit" test for defining a substantial utility. Clearly, the cleavage of carotene or β-carotene to form vitamin A or retinal provides a public benefit. In addition, the generation of RNA probes, antibodies, and transgenic plants using the polynucleotides and polypeptides of the claimed invention all provide a significant public benefit, *i.e.*, the availability of new methods and reagents for making vitamin A for man and animals.

Moreover, the application also states that "***carotene can be conveniently cleaved enzymatically using a protein of the present invention.***" (Specification, p. 11, lines 18-19). And, the application provides an assay for verifying the activity (*i.e.*, cleavage of β-carotene to retinal) of the protein. (*Id.* at p. 25, lines 9-12 and Figs. 7 and 8). Further, the application discloses that "[v]itamin A is essential for man and animal

[1] In this regard, we note that the enzyme with the amino acid sequence of SEQ ID NO:1 produces two moles of retinal from β-carotene just as the disclosure states. (*See* page 5, lines 24-25). There is ***no***

and is largely formed in most organisms from its precursor carotenoids." (*Id.* at p. 5, lines 13-14). In short, the specification discloses a biological activity (cleavage of β-carotene to retinal), identifies an assay for verifying biological activity, and correlates the disclosed activity with a therapeutic application (production of vitamin A for man and animals). Nothing more is required to comply with the utility provision of §101.

As is well settled, an applicant need only make ***one*** credible assertion of a specific utility for the claimed invention to satisfy 35 USC §§101 and 112; additional statements of utility even if not credible, do not render the claimed invention lacking in utility. *See e.g., Raytheon v. Roper*, 220 USPQ 592, 598 (Fed. Cir. 1983) *cert. denied*, 469 US 835 (1984) ("When a properly claimed invention meets ***at least one stated objective***, utility under 35 U.S.C. 101 is clearly shown."); *In re Gottlieb*, 140 USPQ 665, 668 (CCPA 1964) ("Having found that the antibiotic is useful ***for some purpose***, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful.").

In view of the foregoing case law, we submit that the ***nine*** assertions of utility identified above clearly set forth at least one substantial, practical, and credible utility for the presently claimed invention. Thus, it is irrelevant to the question of utility that recent experimental data have revealed that the polypeptide defined by SEQ ID NO:1 should be named as a "monooxygenase" instead of a "dioxygenase" as recited in the specification. However SEQ ID NO:1 is named (*i.e.*, dioxygenase vs. monooxygenase) does not alter the fact that the substrate, the substrate specificity, and the cleavage product identified in the specification for this enzyme remain the same.

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difference in the product or amount of product formed.

(*See* Response to Office Action, Including Amendment mailed July 31, 2001 at p. 4). Moreover, the naming of SEQ ID NO:1 as a "dioxygenase' does not change the fact that the specification also identifies the utility of the "claimed polypeptides" as enzymatically cleaving β-carotene to retinal, which is a step in the vitamin A pathway. As noted above, this assertion of utility alone is sufficient to comply with the utility requirement of §101, notwithstanding the mistaken naming of SEQ ID NO:1.

For the reasons set forth above withdrawal of the rejection of claims 6-36, respectfully is requested.

§112, First Paragraph Rejection

Claims 6-36 were rejected under 35 U.S.C. §112, first paragraph. (Paper No. 11 at 3). In making the rejection, the Examiner asserted that "[s]ince the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation." (*Id.* at 4). The Examiner also asserted that "the function of a polypeptide is unpredictable from its structure and the functionality of a polypeptide must be known in order to use the polypeptide." (*Id.*). The Examiner then concluded that "the specification does not teach how to use SEQ ID NO:1 and DNA molecules encoding SEQ ID NO:1 without undue experimentation." (*Id.*).

For the reasons set forth below, this rejection is respectfully traversed.

All of the arguments set forth above with respect to the §101 rejection are equally applicable to this rejection, and are hereby incorporated by reference. In view of the arguments presented above, it is respectfully submitted that the how-to-use prong of §112, first paragraph is fully met.

In particular, the specification discloses that "[a] process is also provided for the production of vitamin A." (p. 2, line 21). The specification defines vitamin A as "a class of compounds including retinal, retinol, 3-dehydroretinol, retinoic acid, the isomers from these compounds as well as retinylesters." (p. 1, lines 14-16). The specification further discloses that vitamin A is formed from its "precursors carotenoids" (p. 5, lines 13-14) and that "carotene can be conveniently cleaved enzymatically using ***a protein of the present invention***" (p. 11, lines 18-19). The specification identifies both the nucleotide sequence (SEQ ID NO:2) and its encoded polypeptide sequence (SEQ ID NO:1).

The rejection has not contended that SEQ ID NO:1 is not a protein of the present invention or that SEQ ID NO:2 does not encode a protein of the present invention. Thus, it is uncontested that the polypeptide defined by SEQ ID NO:1 is a protein of the present invention. As a protein of the present invention, the specification explicitly states that it cleaves β-carotene to form retinal, which is a part of the vitamin A pathway.

The rejection also does not explain why one skilled in this art, based on the disclosure in the application, would not know how to use SEQ ID NO:1 to cleave β-carotene as a step in producing vitamin A. The specification clearly discloses how to

make SEQ ID NO:2 and to use it to express SEQ ID NO:1. The specification clearly identifies the substrate for the polypeptide encoded by SEQ ID NO:1 (β-carotene), the substrate specificity, and the cleavage product (*see e.g.*, Example 8 and Figs. 7 and 8). In view of the foregoing disclosures, it is respectfully submitted that the how-to-use prong of §112 first paragraph is fully met.

For the reasons set forth above, withdrawal of the rejection of claims 6-36, respectfully is requested.

§102(b) Rejection

Claims 7-9 were rejected under 35 U.S.C. §102(b) by Thorbjornsen, "*Solanum tuberosum* phosphoglycerate kinase precursor, mRNA, nuclear mRNA encoding chloroplast protein, complete cds," (NCBI Abstract submitted 19-Jun-1998) ("Thorbjornsen"). (Paper No. 11 at 4).

In making the rejection, the Examiner asserts that Thorbjornsen teach a DNA molecule that comprises bases 1-36 of SEQ ID NO:2. The Examiner then concludes that Thorbjornsen anticipates claims 7-9. (*Id.*).

With a view toward furthering prosecution, claim 7 has been amended to remove the recitation of "or a fragment thereof" and claims 8 and 9 have been amended to recite that the "at least 20" (claim 8) or the "at least 30" (claim 9) bases of SEQ ID NO:2 are from its coding region. In view of these amendments, the overlapping 36 nucleotides disclosed by Thorbjornsen are excluded from the amended claims.

In view of the foregoing, withdrawal of the rejection of claims 7-9, respectfully is requested.

For the reasons set forth above, favorable action on the merits including reconsideration, entry of the amendments, withdrawal of the rejections, and allowance of all the claims, respectfully, is requested. If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Box AF, Commissioner for Patents, Washington, DC 20231, on February 28, 2002.

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Respectfully submitted,

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"Marked Up" Amendments to Claims Pursuant to Rule 1.121(c)

7. (Amended) An isolated nucleic acid sequence according to claim 6 which comprises SEQ ID NO:2 [or a fragment thereof].

8. (Twice Amended) An isolated nucleic acid sequence comprising at least 20 bases of the coding region of SEQ ID NO:2 or at least 20 bases of the nucleic acid sequence that encodes SEQ ID NO:1.

9. (Twice Amended) An isolated nucleic acid sequence comprising at least 30 bases of the coding region of SEQ ID NO:2 or at least 30 bases of the nucleic acid sequence that encodes SEQ ID NO:1.

36. (Twice Amended) A kit for amplifying and/or detecting a polypeptide having an amino acid sequence defined by [or fragment thereof encoding the polypeptide of] SEQ ID NO:1 or a fragment thereof, the kit comprising at least one primer selected from the group consisting of SEQ ID NOs:8, 9, and 10.